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Preparation of cross-linked aliphatic polyester and application to thermo-responsive material

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Abstract

The aim of this study is to investigate the application of a crystalline polymer network to a thermo-responsive material. To achieve this purpose, cross-linked aliphatic polyesters containing a poly-ϵ-caprolactone (poly-CL) segment were prepared from tetrafunctional star-shaped macromonomers. The macromonomers were synthesized by ring-opening polymerization of CL and *L*-lactide (LA) initiated with pentaerythritol followed by condensation with methacryloyl chloride to introduce a functional group at the chain ends. The cross-linked polyester membranes were prepared by way of a radical polymerization of the macromonomers with visible light irradiation in the presence of initiator and sensitizer. The obtained materials, which consisted of CL homopolymer and LA/CL block copolymer, exhibited a phase transition temperature derived from the melting of poly-CL segment. The transition temperatures of the macromonomers and the corresponding cross-linked polyesters depended on the length of poly-CL segment. In order to examine the thermo-responsive properties, the permeation of a model drug, indomethacin, through the membrane composed of cross-linked polyester was investigated by using a 2-chamber diffusion cell. The permeability of the drug increased steeply at around the phase transition with increasing temperature. In addition, the relationship between the degree of crystallinity and the increase of the drug permeability was discussed. From the analysis of permeation profiles, it was revealed that the partition of the drug from the donor phase to the membrane surface considerably increased above the phase transition. Also, the reversible control of the drug permeation through the membrane in response to the repeating temperature change (20°C and 40°C) was observed.

Keywords: Aliphatic polyester; Macromonomer; Phase transition; Thermo-responsive material; Permeation, indomethacin

1. Introduction

A temperature-sensitive drug delivery system using a polymeric material, which is responsive to temperature changes, is capable of releasing the drug when required. For example, it is very effective that an antipyretic agent is released only when a patient has fever or when an external heat is applied. As typical thermo-responsive materials, gels, copolymers and interpenetrating polymer network (IPN) of which the component is mainly poly-N-isopropylacrylamide can be illustrated [1]. For these polymeric materials, the control of the drug release is achieved by shrinking or swelling of the materials according to hydration and dehydration of poly-N-isopropylacrylamide at around the transition temperature. In addition, materials consisting of porous film or polylactide microsphere entrapped with liquid-crystalline molecules were prepared, and the drug permeation or the temperature-controlled release was investigated. [2–5] In the case

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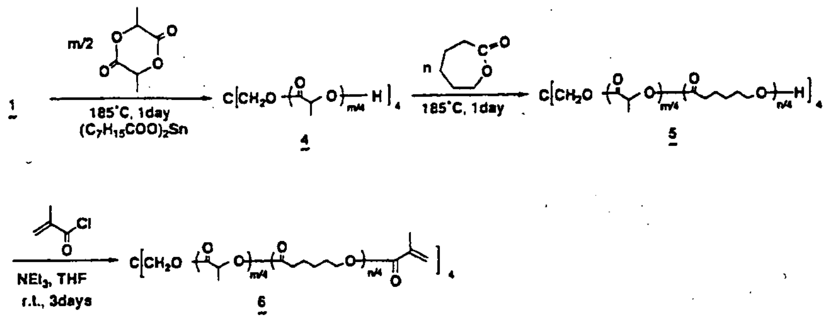
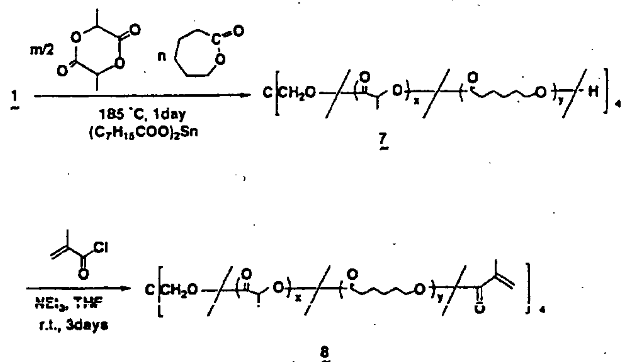


Scheme 2. Preparation of macromonomers composed of LA/CL block copolymer.



Scheme 3. Preparation of macromonomers composed of LA/CL random copolymer.

TEA were added to the solution, and the mixture was stirred for 3 days at room temperature under an argon atmosphere. After removing the solvent, unreacted methacryloyl chloride and excess TEA by evaporation, the residue was dissolved in ethyl acetate, and the precipitated salt, TEA·HCl, was separated by filtration. The filtrate was concentrated and reprecipitated into an excess amount of a mixed solvent of hexane/diethyl ether/methanol (18/1/1 by volume), to afford 74.2 g of the tetrafunctional macromonomer 3 as a white powder (yield 88.7%). ^{1}H-NMR chemical shifts were as follows: ^{1}H-NMR, δ ($CDCl_3$, ppm); 1.58 (m, -$CH_2(CH_2)_3CH_2O$-), 1.90 (s, -$C(CH_3)=CH_2$), 2.31 (t, -$COCH_2$-), 4.06 (t, -CH_2O-), 5.58 (d, -$C(CH_3)=CH_2$), 6.12 (d, -$C(CH_3)=CH_2$).

The total average degree of polymerization n of each branch of 3 was determined by ^{1}H-NMR to be about 76. The degree of polymerization could be controlled by adjusting the ratio of CL and PE in the above reaction.

The macromonomers consisting of LA/CL block and random copolymers (poly-LA-*b*-CL and poly-LA-*r*-CL) were prepared by the similar procedure as above, the synthetic diagrams of which were procedure represented in Schemes 2 and 3.

2.3. Preparation of cross-linked polyesters

1.00 g of each of the tetrafunctional star-shaped macromonomers 3, 6 and 8, 0.01 g of *N,N*-dimethyl-*p*-toluidine and 0.01 g of camphorquinone were dissolved in 1.00 g of xylene. A spacer made from Teflon® having a thickness of 0.1 mm was inserted between two glass plates having a size of 10 cm × 10 cm, and the above-prepared xylene solution was injected into the space between the glass plates. The glass plates were uniformly irradiated with visible light (α-LIGHT, LCR-1, J. Morita Co., Japan) at an intensity of about 0.5 mW/cm^2 for 10 minutes, to obtain a colorless transparent membrane having a thickness of about 0.1 mm. The membrane was immersed in acetone for about 8 hours to remove the initiator and sensitizer contained wherein, and then thoroughly dried under reduced pressure.

Table 1
Characterizations of macromonomers composed of branched aliphatic polyesters

Code	Chemical structure[a]	m/n[b]	x/y[c]	Mw[d]	Mw/Mn[d]	Yield (%)
3a[e]	3	0/9	–	2,780	1.55	78.6
3b[e]	3	0/19	–	6,900	1.45	78.2
3c[e]	3	0/38	–	10,200	1.39	98.1
3d[e]	3	0/78	–	20,500	1.99	88.7
3e[e]	3	0/116	–	48,700	1.51	88.7
6a[f]	6	20/28	–	7,470	1.46	87.7
6b[f]	6	20/75	–	11,600	1.36	87.2
6c[f]	6	20/117	–	16,700	1.39	89.8
6d[f]	6	40/55	–	13,900	1.39	96.8
6e[f]	6	80/91	–	13,300	1.68	85.6
8a[g]	8	–	11/8	4,660	1.44	78.4
8b[g]	8	–	9/20	4,810	1.47	85.1
8c[g]	8	–	5/32	9,660	1.41	98.7
8d[g]	8	–	11/80	13,900	1.25	94.3
8e[g]	8	–	16/80	15,000	1.27	73.4

[a] See Schemes 1, 2 and 3.
[b] "m" and "n" mean the average degree of polymerization of LA and CL, which were determined by ^{1}H-NMR.
[c] Composition (molar ratio) of LA/CL random copolymers.
[d] These value were determined by GPC with PSt standard in THF.
[e] 3a–3e are macromonomers composed CL homopolymer.
[f] 6a–6e are macromonomers composed of LA/CL block copolymer.
[g] 8a–8e are macromonomers composed of LA/CL random copolymer.

the cross-linked material composed of poly-LA-*b*-CL also exhibited an excellent thermo-responsive property as well as the material containing only poly-CL.

The macromonomers were prepared by condensation of each hydroxy-terminated polyester with methacryloyl chloride. The characterizations of the obtained macromonomers are summarized in Table 1. The segment length of each component was controlled by changing the ratio of monomer to initiator in the above polymerization reaction. Then, the radical polymerizations of the macromonomers of which the structures were represented as **3**, **6** and **8** were carried out by a visible light irradiation between two glass plates in the presence of radical initiator and sensitizer. In this reaction, the cross-linking by radical polymerization and the preparation of membrane proceeded at the same time. This method was very useful to obtain the membrane of the uniform thickness and to control the thickness of the membrane only by changing the thickness of the spacer between the glass plates. Actually, tough membranes containing each aliphatic polyester segment with an uniform thickness, about 100 μm, were obtained by this method.

3.2. Thermal behavior of the macromonomers and cross-linked membranes

Figs. 1(a and b) show DSC curves of the star-shaped macromonomers and the cross-linked compounds, respectively, which consisted of poly-CL homopolymer. These macromonomers exhibited the phase transition derived from their melting, and the temperatures (Tm) and enthalpies (ΔH) of melting depended on the degree of polymerization of CL segment, as shown in Fig. 1(a). After the cross-linking, Tm shifted to lower temperature and ΔH values decreased as compared with the corresponding macromonomer, as indicated in Fig. 1(b). Table 2 lists the degree of crystallinity of the macromonomers and the corresponding cross-linked materials, which was obtained by the calculation from the ratio of ΔH of the materials and poly-CL homopolymer (134.9 J/g) [14]. As shown in Table 2, the decrease of ΔH by cross-linking reaction reflected the depression of crystallinity. It

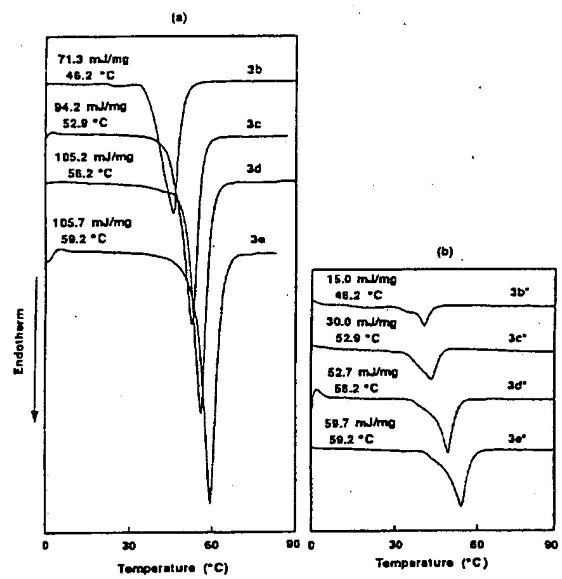


Fig. 1. DSC curves of (a) macromonomers and (b) the corresponding cross-linked compounds composed of poly-CL. **3b***, **3c***, **3d*** and **3e*** represent the cross-linked polyesters prepared from **3b**, **3c**, **3d** and **3e**, respectively.

r-CL exhibited no phase transition, even though the corresponding macromonomer **8d** showed a clear melting peak in the DSC curve. Because the reactivity of LA was surely lower than that of CL in the ring-opening copolymerization of CL and LA, the sequence of CL and LA monomers in the poly-LA-*r*-CL macromonomer might not be perfectly random, and the sequence of $(CL)_n$ was probably present in the copolymer to some extent. This sequence might contribute to exhibit the phase transition in the poly-LA-*r*-CL macromonomers. After the cross-linking, however, the phase transition behavior was not observed because the sequence of $(CL)_n$ was too short to exhibit the phase transition.

3.3. Permeation of indomethacin through the cross-linked polyester membrane

Fig. 4(a) shows the permeation profiles of indomethacin through the cross-linked membrane composed of poly-CL homopolymer (**3d***) in the range between 20°C and 55°C in a step of 5°C. The permeation of the drug was very little until 35°C, and then, it increased steeply at temperatures exceeding 40°C. The drastic change of the drug permeation at around 35°C was obviously due to the phase transition of poly-CL segment in the membrane. This tendency was also observed for the membrane composed of poly-LA-*b*-CL. On the other hand, in the case of the membrane composed of poly-LA-*r*-CL (**8d***), the permeation of the drug increased monotonously with increasing temperature, as represented in Fig. 4(b). In Table 3, the temperature range indicating the maximum increase of permeability and its ratio of the permeability at the two temperatures is listed as compared with the crystallinity of each compound. As shown in the table, the large increase of permeability was observed on the compounds which exhibited the high crystallinity. It was suggested that the cross-linked polyester membrane containing more than about 40% of crystallinity could control the permeation of the drug, such as indomethacin, in response to the temperature change. To achieve the precise ON-OFF control, the material containing much higher crystallinity will be preferable, because the substance can permeate through the amorphous

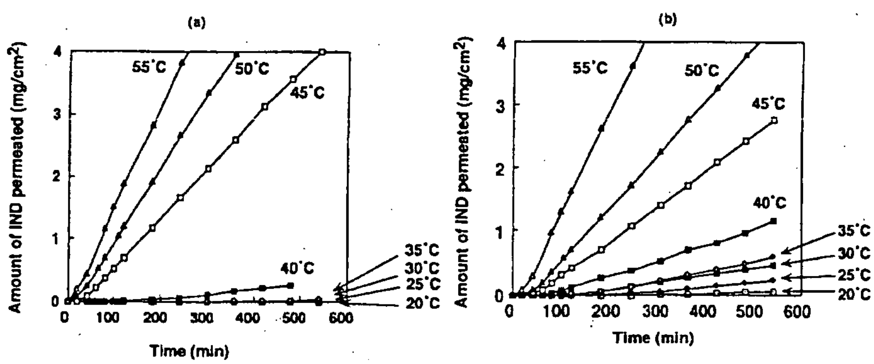


Fig. 4. The effect of temperature on the permeation of indomethacin through the cross-linked membranes composed of poly-CL (**3d***) and poly-LA-*r*-CL (**8d***).

Table 3
Relationship between the crystallinity of the cross-linked materials and the drug permeability

compound	crystallinity (%)	temp. range indicating maximum increase of drug permeability (°C)	increase of drug permeability[a] (–)
3c*	22.2	35–40	2.7
3d*	39.1	40–45	8.9
6b*	41.2	40–45	8.1
8d*	–	35–40	1.9

[a]The value indicated the ratio of permeation coefficients at the two temperatures in this table.

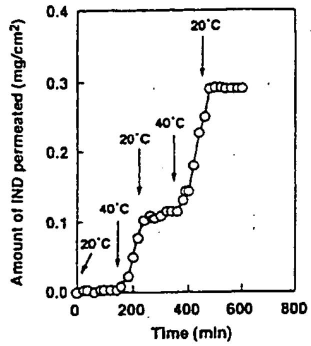


Fig. 7. Permeation profile of indomethacin through the cross-linked membrane composed of poly-LA-*b*-CL (**6b***) in response to repeating temperature change.

drug permeation in response to repeating temperature change, another permeation experiment was carried out by using the membrane composed of poly-CL-*b*-LA (**6b***). The permeation profile of the drug through the membrane with temperature change was shown in Fig. 7. As indicated in the figure, the membrane could respond to the repeating temperature change and the pulsating permeation of the drug was observed. The similar control of the drug permeation was also observed for the membranes composed of poly-CL homopolymers (**3d*** and **3e***). The sensitivity of thermo-response of the materials would be influenced by the rate of the transition between the both phases. Although the precise rate could not be obtained, the fact that these membranes showed the pulsating permeation in response to repeating temperature change indicated the quick reversible transition of crystalline and amorphous phases.

4. Conclusion

Novel type of thermo-responsive membranes were prepared, which were based on the distinct phase transition of aliphatic polyester network containing a long poly-CL segment. The membranes achieved the reversible control of drug permeation in response to the repeating temperature change. It seemed that the considerable variation of the drug permeability below and above the phase transition temperature was due to the significant alteration of the partition of drug on the membrane surface. This material might be available to fabricate the drug delivery system capable to response to the temperature change.

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